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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/992,643	11/14/2001	David Botstein	P2730P1C13	4960

35489 7590 08/15/2005

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EXAMINER	
KEMMERER, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 08/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/992,643	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-126 and 129-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-126 and 129-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/3/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03 June 2005 has been entered.

The request to change inventorship received 27 January 2005 has been granted.

Claims 1-118, 127, and 128 are canceled. Claims 119-126 and 129-131 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The rejection of claims 130 and 131 under 35 U.S.C. § 1 12, first paragraph, regarding adequate written description, is *withdrawn* upon further consideration.

35 U.S.C. §§ 101 and 112, First Paragraph

Claims 119-126 and 129-131 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

Claims 119-126 and 129-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The basis for these rejection is set forth in the previous Office Actions. See, for example, the non-final rejection mailed 25 February 2004.

Applicant's arguments (pp. 5-17 of the preliminary amendment received 03 June 2005) have been fully considered but are not fond to be persuasive for the following reasons. Applicant reviews the legal standard for patentable utility, with which the examiner takes no issue.

Applicant argues that the gene amplification assay is well-described in Table 8, showing that nucleic acids encoding PRO1112 were significantly overexpressed in lung adenocarcinoma tumors and some colon tumors as compared to the normal control, providing a patentable utility for the nucleic acids encoding PRO1112 and their variants. This has been fully considered but is not found to be persuasive. While the data in Table 8 may provide a basis for utility and enablement of PRO1112 nucleic acid, it does not provide a basis for utility or enablement of the claimed polypeptides. The art supports this position by

establishing that there is no strong correlation between gene amplification and increased mRNA or protein levels. See Haynes et al., Pennica et al., Konopka et al. of record. Furthermore, the art recognizes that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy before the epithelial cells turn cancerous. See Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12), who teach that damaged, precancerous lung epithelium is often aneuploid. See especially p. 4, Figure 4. The gene amplification assay does not provide a comparison between the lung tumor samples and normal lung epithelium, or between colon tumor samples and normal colon tissue, and thus it is not clear that PRO1112 is amplified in cancerous lung or colon epithelium more than in damaged (non-cancerous) lung or colon epithelium. One skilled in the art would not conclude that PRO1112 is a diagnostic probe for lung or colon cancer unless it is clear that PRO1112 is amplified to a clearly greater extent in true lung or colon tumor tissue relative to non-cancerous lung or colon epithelium. Also, while it might be argued in hindsight that PRO1112 would still be a marker at least for precancerous, or damaged, lung or colon epithelium, such is not suggested by the specification as originally filed and is not well-established in the *prior* art. Furthermore, even if it could be established that gene amplification is reflected by increased polypeptide levels, the claims are broadly drawn to polypeptides that can be variants of the polypeptide of SEQ ID NO: 207, including fragments and substitution variants. One skilled in the art would expect that such variant sequences would not reasonably be expected to show changed levels for a particular disease state.

Applicant criticizes Pennica et al. and Konopka et al. as being limited to only one gene. This has been fully considered but is not found to be persuasive. Pennica et al. and Konopka et al. constitute evidence that one skilled in the art cannot assume that any one gene's amplification results in protein over-expression. The issue at hand also concerns only one gene and the protein it encodes.

Applicant criticizes Haynes et al., stating that there is no legal requirement to establish a necessary or strong correlation between an increase in copy number of mRNA and protein expression levels. Applicant argues that the issue is whether or not it is more likely than not that a person of ordinary skill in the pertinent art would recognize a positive correlation between mRNA expression levels and protein expression levels. Applicant argues that there is a positive correlation between most of the 80 proteins studied by Haynes et al. Applicant argues that Haynes et al. is not relevant because it is limited to yeast genes, not human genes. Applicant argues that Haynes et al. failed to compare mRNA expression levels and protein expression levels in the same yeast cells. Applicant concludes that the reliance on Haynes et al. is misplaced, since it shows a general trend between mRNA and protein levels, and that an improper, heightened legal standard has been applied. This has been fully considered but is not found to be persuasive. Haynes et al. clearly conclude that, "even for a population of genes predicted to be relatively homogeneous with respect to protein half-life and gene expression, the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript" (p. 1863, section

2.1). Regarding the relevance of yeast genes, Applicant is directed to Lian et al. (2001, Blood 98:513-524) who show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract). The evidence as a whole clearly indicates that one skilled in the art would not assume that an increase in gene copy number would correspond with an increase in mRNA levels or protein levels without doing the empirical experimentation necessary to measure mRNA and protein levels. The requirement for such empirical experimentation indicates that the asserted utility for the claimed polypeptides is not substantial; it is not in currently available form.

Applicant argues that Table 9A showed Ct increases in several lung and colon tumor samples, wherein the increases would not be considered small by those in the art. Applicant urges that the increases are significant and correlate well with diagnosis of cancer, thus providing a "specific benefit in currently available form." Applicant argues that the "substantial utility" requirement should not be interpreted as requiring "immediate benefit to the public," but rather that products or services based on the claimed invention must be "currently available" to the public. This has been fully considered but is not found to be persuasive. First, the specification in Example 170 does not assert that the utility of the

claimed *proteins* (or their antibodies) lies in their use as diagnostics. The specification states that the DNA molecules can be used in cancer diagnostics, but the proteins and antibodies can be used to develop cancer therapeutics. The instant claims are directed to polypeptides, not genes. Nevertheless, the claimed proteins also cannot be used as cancer diagnostics regardless of what the DNA data are because a change in gene copy number does not reliably correlate with a change in polypeptide expression levels, as evidenced by the references cited herein. Furthermore, Table 9 reports a comparison of lung or colon tumor tissue samples with a pooled sample of DNA from normal cells, but not matched tissue samples (i.e., normal lung epithelium tissue or normal colon tissue). The art uses matched tissue samples as a rule when evaluating whether or not a protein can be used as a diagnostic for cancer, indicating that the art does not consider pooled, unrelated DNA samples to be an appropriate control. See Hu et al. (2003, Journal of Proteome Research 2:405-412) and Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313).

Applicant discusses the Orntoft, Hyman and Pollack references. Orntoft et al. (Molecular and Cellular Proteomics 1:37-45, 2002) could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract.) It would appear that applicants have provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Hyman (Cancer Research 62:6240-6245) found 44% of *highly* amplified genes showed

overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO1112 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification.

Applicant refers again to the Polakis declaration, and argues that the examiner's criticism of the declaration for failing to provide data is improper. However, given the evidence in the art that increased DNA amplification does not necessarily correlate with increased mRNA levels, and that increased mRNA levels do not necessarily correlate with increased protein levels, the examiner maintains that one skilled in the art would view the instant gene amplification data as merely preliminary with regard to whether or not mRNA or protein levels of PRO1112 are specifically amplified in tumors. Further research would have to be done in order to determine if PRO1112 mRNA and protein are amplified and, if so, whether or not the amplification is significant enough to indicate PRO1112 protein as a cancer marker. Thus, the claimed invention does not provide products or services in "currently available" to the public.

Applicant argues that the examiner must accept an opinion from a qualified expert. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant case, the nature of the fact is whether or not there is a correlation between mRNA levels and protein levels. There is strong opposing evidence that there is no strong correlation between the two. The expert has a strong interest in the outcome of the case, as Dr. Polakis is employed by the assignee. Finally, while Dr. Polakis refers to his experiments, only conclusions were set forth in the declaration. No data or results were presented for independent analysis. In view of the totality of the evidence, including the declarations submitted under 37 CFR 1.132 and the publications of record, the instant utility rejection is appropriate.

Applicant criticizes the examiner's reliance on Hu et al. Applicant argues that Hu et al. is not relevant, as it does not discuss gene amplification. Applicant criticizes Hu et al. as being base don a statistical analysis of information published in the literature. This has been fully considered but is not found to be persuasive. The asserted utility for the claimed polypeptides is based on a

sequence of presumptions. First, it is presumed that gene amplification predicts increased mRNA production. Second, it is presumed that increased mRNA production leads to increased protein production. Hu et al. is directly on point by showing that the second presumption is incorrect when designating proteins as diagnostic markers for cancer. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). The instant specification does not disclose that PRO1112 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu et al., the skilled artisan would not reasonably expect that PRO1112 protein can be used as a cancer diagnostic. Furthermore, Applicant's attention is directed to Hanna et al. (of record, Pathology Associates Medical Laboratories, 1999), who show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The instant specification does not provide this additional information, and thus the skilled artisan would need to perform additional

experiments. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

Applicant criticizes Hu et al. as using faulty statistical analysis. This has been fully considered but is not found to be persuasive. Applicant is holding Hu et al. to a higher standard than their own specification, which does not provide proper statistical analysis such as reproducibility, standard error rates, etc.

Applicant points to the declaration of Dr.. Ashkenazi, submitted under 37 CFR 1.132 on 25 June 2004, as establishing that, even is the protein were not over-expressed, the simultaneous testing of gene amplification and gene product over-expression would enable more accurate tumor classification. However, while this may be true, the specification does not disclose such further testing of gene product over-expression. Therefore, the skilled artisan would have been required to do the testing. In view of such requirement, the products or services based on the claimed invention are not in "currently available" form for the public.

Applicant concludes that the gene amplification assay provides a credible, specific and substantial utility for the claimed polypeptides because it is more likely than not that a gene amplified in cancer correlates with an over-expressed encoded protein. Applicant argues that none of the references address the standard for genes or gene classes in general, or provide statistical analysis. Applicant asserts that the evidence supports that it is more likely than not that gene amplification predicts protein over-expression. This has been fully considered but is not found to be persuasive. Again, it is important to note that the specification does not actually assert that the claimed polypeptides can be

used as cancer diagnostics in Example 170. Rather, it is asserted that the polypeptides or their antibodies can be used to develop cancer therapeutics. However, this asserted utility is not substantial, since the specification does not provide a clear nexus between PRO1112 and cancer occurrence or progression, for reasons noted above. Furthermore, the evidence of record clearly indicates that a small increase in gene amplification does not correlate well with protein over-expression, for reasons noted above in the discussions of the individual references. Thus, the preponderance of the art supports the *prima facie* finding that a minor amplification of DNA would not form the basis for a substantial assertion of an association between PRO1112 protein and cancer.

Claims 119-123 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis of this rejection is set forth at pp. 7-9 of the Office Action mailed 25 February 2004. Furthermore, the claims are directed to isolated "native sequence" polypeptides having at least 80%-99% identity to SEQ ID NO: 207, wherein the nucleic acid encoding the polypeptide is amplified in lung tumors. The specification discloses a single amino acid sequence for PRO1112, SEQ ID NO: 207. There is a utility and enablement issue regarding whether or not the nucleic acid encoding PRO1112 is amplified in lung tumors (see rejections under

35 U.S.C. §§ 101 and 112, first paragraph, above). Furthermore, the specification does not disclosure any variants of SEQ ID NO: 207, naturally occurring or not, nor whether such sequences are amplified in lung tumors.

Applicant's arguments (pp. 17-19, remarks submitted 03 June 2005) have been fully considered but are not found to be persuasive for the following reasons.

Applicant discusses the legal test for written description, with which the examiner takes no issue.

Applicant argues that the specification provides reduction to practice of a full-length PRO1112 polypeptide of SEQ ID NO: 207, with or without its signal sequence. Applicant urges that such provides basis for the claimed genus of native polypeptide sequences with at least 80-99% sequence identity to SEQ ID NO: 207 which are functionally defined as being encoded by a nucleic acid that is amplified in lung or colon tumors. Applicant points to the specification's disclosure of methods for the determination of percent identity, and assays for identification of nucleic acids and for the functional limitation in the claims. Applicant urges that the skilled artisan can readily test native polypeptide sequences for identity and whether or not the encoding nucleic acids are amplified in lung or colon tumors. This has been fully considered but is not found to be persuasive. The courts have specifically stated that if the skilled artisan cannot envision the *detailed chemical structure* of an encompassed polypeptide, until the structure is disclosed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of

the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In the instant case, SEQ ID NO; 207 has been disclosed, but no native sequence variants thereof have been disclosed regardless of whether or not they are encoded by nucleic acids that are amplified in tumors. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factors present in the claim are a partial structure in the form of a recitation of percent identity, and a requirement that the encoding nucleic acids are amplified in lung or colon tumors. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

ECK